ACTA ONCOLOGICA
2023, VOL. 62, NO. 6, 565–570
https://doi.org/10.1080/0284186X.2023.2216338

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LETTER TO THE EDITOR

BAP1 genetic testing among melanoma and cancer-prone families in Sweden

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ARTICLE HISTORY Received 20 March 2023; Accepted 16 May 2023

Background

The BRCA1-associated protein-1 (*BAP1*) gene has in the recent years been identified as a critical driver gene in the pathogenesis of many tumors [1,2]. The *BAP1* gene is located on chromosome 3 (3p21.31-p21.2), where its 17 exons transcribe into the 729 amino acids long BAP1 protein [3]. BAP1 has been categorized as a tumor suppressor, and has roles in numerous cellular processes, including DNA damage response, cell cycle regulation, cell growth, metabolism, and the regulation of inflammatory responses [1,3,4]. It is known to bind to a number of proteins *via* specific domains, including BRCA1, BARD1, ASXL1/2, HCFC1, YY1, and FOXK1/2 (11) as indicated in Figure 1 [3,5,6]. *BAP1* is frequently mutated or lost in several tumor types, including uveal melanoma (UM), cholangiocarcinoma, renal cell carcinoma (RCC), mesothelioma, and bladder cancer [2,7]. Somatic loss of *BAP1* in tumors is also in many tumors associated with a poor outcome [8–10]. The first report of a germline pathogenic variant (PV) in *BAP1* was published in 2011 [8]. Subsequent reports described inactivating germline PVs segregating in cancer-prone families, mainly characterized by distinct melanocytic tumors and mesothelioma in combination with other cancers [11–14]. The neoplasms associated with *BAP1* germline PVs, also called the *BAP*1 tumor predisposition syndrome (TPDS), has been defined to include the core tumors cutaneous melanoma (CM), UM, RCC, pleural and peritoneal mesothelioma, meningioma, basal cell carcinoma (BCC), and BAP1-inactivated melanocytic tumor (BIMT) [11,15–17]. BIMTs or informally BAPomas are skin-colored to reddish-brown papules that have characteristic clinical and dermatoscopic features and a unique melanocytic pathology [13,18]. Here, we report of the *BAP1* germline genetics testing in melanoma and cancer-prone families in Sweden that has been ongoing since the identification of the first carrier family in 2012.

Material and methods

Patients and families

After the identification of the first family in Sweden with a *BAP1* PV in 2012, germline sequencing of the *BAP1* gene has been offered to families presenting with *BAP1* core tumors. Essentially, this has been performed in families with CM in combination with any other *BAP1* core tumor in the first- or the second-degree relatives (UM, BIMT, mesothelioma, meningioma, or RCC). Also, families with two or more cases of UM or UM in combination with any other *BAP1* core tumor in the first- to the second-degree relatives have been tested. Similarly, families with *BIMTs* in combination with any other *BAP1* core tumor has been tested. Families with suspected *BAP1* tumor syndrome were on a national level, referred to the Hereditary melanoma clinic at Karolinska University hospital in Stockholm, where the test has been performed. In addition, since 2019, all 'regular' CM families in Stockholm (i.e., without *BAP1* core tumors) have undergone *BAP1* testing as it has been implemented in routine gene panel testing for familial melanoma (including also *CDKN2A* and *CDK4*). For this testing, familial melanoma has been defined as three or more cases of CM in a family or two CM cases if one case is <55 years at diagnosis. At the hereditary melanoma clinic, a pedigree has been established and diagnoses verified by pathology or clinical records and if the criteria for genetic testing is fulfilled, a test has been offered to affected members. Descriptive statistics were applied to demonstrate the occurrence of *BAP1 PVs* in association with tumor spectrums in the families. The study was approved by the Swedish Ethical Review Authority (Dnr. 2012/1192-32 and 2018/803-31).

BAP1 *germline genetic testing*

Until December 2018, genomic DNA was analyzed for genetic variation in the *BAP1* gene in a research laboratory with

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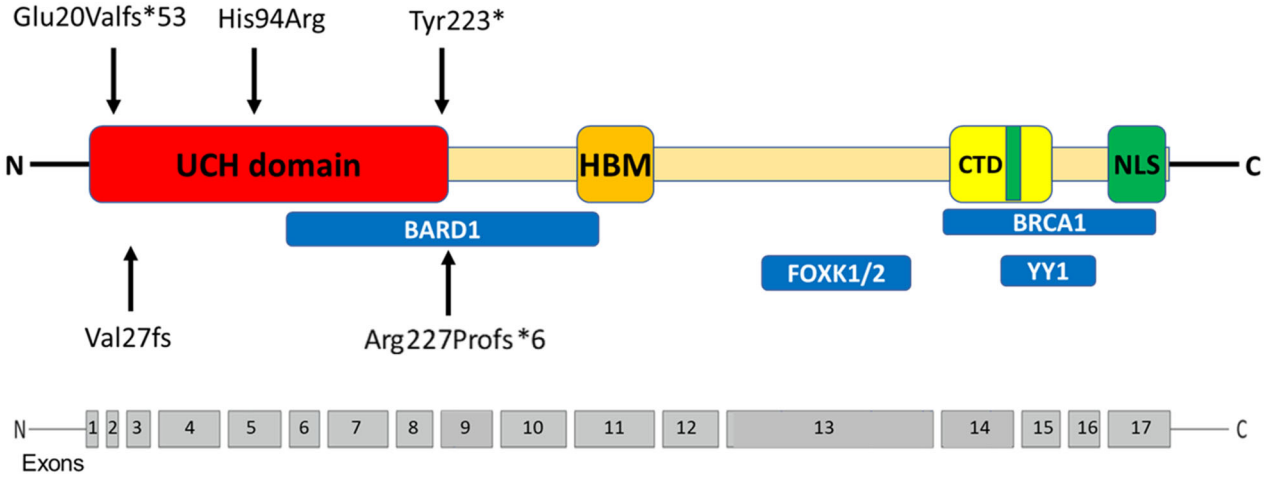
Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2216338.



cDNA change	Protein change	Families w. variant (N)	Exon	Chromosome position (bp)	ACMG rating	ACMG evidence[1]	ClinVar ID
c.58_59insTG	p.(Glu20Valfs*53)	3	2	52409723	Pathogenic	PVS1, PM2, PM4, PP1, PP4	1749775
c.79insG	p.(Val27fs)	1	3	52409596	Pathogenic	PVS1, PM2, PM4, PP1, PP4	473745
c.281A>G	p.His94Arg	1	5	52408052	Likely pathogenic[2]	PM2, PP3, PP1, PP4, PM1, PS3	480852
c.669C>A	p.(Tyr223*)	1	9	52406367	Pathogenic	PVS1, PM2, PM4, PP1, PP4	1071927
c.680_687delins13	p.(Arg227Profs*6)	2	9	52406349	Pathogenic	PVS1, PM2, PM4, PP1, PP4	

Figure 1. Pathogenic variants identified in Sweden, plotted along the BRCA1-associated protein-1 (BAP1) gene with the functional domains shown. Ubiquitin carboxyl hydrolase (UCH) domain; HBM, host cell factor 1 (HCF1) binding domain; nuclear localization signals (NLS); C-terminal domain (CTD), additional sex combs like (ASXL1/2) binding domain; BRCA1-associated RING domain protein 1 (BARD1) binding region; Breast Cancer type 1 (BRCA1)-binding region and Ying Yang 1 (YY1) binding region; Forkhead Box Protein K1/2. [1]American College of Medical Genetics (ACMG) evidence: PVS1 - null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where LOF is a known mechanism of disease. PM1-mutational hotspot, PM2–Absent from controls in Exome Aggregation Consortium (ExAC). PM4–Protein length changes as a result of in-frame deletions/insertions in a nonrepeat region or stop-loss variants. PP1–Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease. PP3–Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc.). PP4–Patient's phenotype or family history is highly specific for a disease with a single genetic etiology. PS3–Functional studies. [2]Functional studies of the missense variant c.281A > G, demonstrated an almost complete abolishment of enzymatic activity (Repo et al. Hum Mol Genet. 2019). This together with a co-segregation of a highly specific phenotype, absence of variant in controls, computational evidence and position in a hotspot gene site gives evidence that the variant is likely pathogenic.

Sanger sequencing (bidirectional). All exons and exon–intron boundaries were covered by the analysis. As of January 2019, the screening was done as a clinical test at an accredited laboratory, the Karolinska University Laboratory. The method used was accredited with a library preparation performed with IonAmpliSeq sequencing with IonS5 and data analysis with IonReporter (Life Technologies, Carlsbad, CA). All the reported gene variants have been detected by both methods. The clinical variant interpretation guidelines from the American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) were used to assess if a variant was (likely) pathogenic, of uncertain significance, or (likely) benign [19].

Results

Incidence of BAP1 *PVs in tested families*

In total, 190 families were tested for *BAP1 PVs*. Of these, 141 were CM families where none of the other *BAP1* core tumors (UM, BIMT, RCC, mesothelioma, or meningioma) have been identified (Table 1). In these families none (0%) were identified with a *BAP1* PV. Among these 141 CM families, none (0%) had *CDK4* PVs while nine (6.4%) had *CDKN2A* PVs (same PVs as previously reported) [20]. There were 49 families that were tested specifically for a suspicion of *BAP1* tumor syndrome (Table 1). *BAP1* PVs were identified in eight (16.3%) of these families. Families with CM, UM, or RCC in family all had similar frequencies of *BAP1* PV (<20%). BIMTs were diagnosed in nine families of which seven (77.8%) carried a germline *BAP1* PV. Mesotheliomas and meningiomas were diagnosed in six and four families of which five (83.3%) and two (50%) had *BAP1* PVs, respectively. In families with BIMT in combination with another *BAP1* core tumor type in family, the frequency of *BAP1* PVs was high (>85%).

PVs and tumor spectrum in BAP1 *carrier families*

Eight families with *BAP1* PVs were identified, of which four have been previously reported [17,21] (Table 2). Of the eight families, seven (87.5%) families had CM in their pedigree, five (62.5%) had UM, seven (87.5%) had BIMT, five (62.5%) had mesothelioma, two (25.0%) had meningioma, and two (25.0%) had RCC, while six families (75.0%) had BCC in their pedigree. The youngest age at diagnosis in the families was, for CM, median 44.5 years (range 20–56 years), for UM 36 years (range 16–40 years), for BIMT 11 years (range 10–51 years), for mesothelioma 52 years (range 39–80 years), for meningioma 50.5 years (range 40–61 years), for RCC 67.5 years (range 66–69 years), and for BCC 52 years (range 39–76 years). Among families with *BAP1* core tumors, tested

Table 1. *BAP1* germline genetic testing in 190 families from Sweden.

Type of family	Families tested for *BAP1*, *N*	Families with *BAP1* PV, *N*	%
Cutaneous melanoma families without other *BAP1* core tumors[a]	141	0	0.0%
Families with *BAP1* core tumors[b]	49	8	16.3%
Cutaneous melanoma (CM) in family	37	7	18.9%
Uveal melanoma (UM) in family	30	5	16.7%
BAP1-inactivated melanocytic tumor (BIMT) in family	9	7	77.8%
Renal cell cancer (RCC) in family	15	2	13.3%
Mesothelioma in family	6	5	83.3%
Meningioma in family	4	2	50.0%
Families with both:			
CM and UM in family	20	4	20.0%
CM and RCC in family	15	2	13.3%
BIMT and CM in family	7	6	85.7%
BIMT and UM in family	4	4	100.0%
BIMT and mesothelioma in family	4	4	100.0%
UM and mesothelioma in family	3	3	100.0%

[a]*BAP1* core tumors (beside cutaneous melanoma); UM: uveal melanoma; RCC: mesothelioma, renal cell cancer; BIMT: meningioma, BAP1 inactivated melanocytic tumor.
[b]Families with *BAP1* core tumors had among probands and the first- and second-degree relatives:
CM in combination with other *BAP1* core tumor(s),
BIMT in combination with other *BAP1* core tumor(s),
UM in combination with other *BAP1* core tumor(s), and
Two or more cases of UM.

negative for *BAP1* PV, the median age at diagnosis of CM was 45 years (range 16–80 years) and for UM 58 years (range 20–72 years). Hence UM were diagnosed in significantly younger members in *BAP1* PV families ($p < .001$), whereas CM were diagnosed at similar ages in carrier and noncarrier families ($p = .594$). Other tumors that were present in the pedigrees of at least two families were breast, pancreatic, prostate, and lung cancer. Highest mortality was seen for mesothelioma, where six of seven cases (83.3%) had died from the disease, the only survivor was diagnosed with a lesion considered to be a mesothelioma precursor. Of the eight cases of UM, four had died from the disease (50%), whereof three deaths were in the same family. Among the 12 cases of CM, only one died from CM (8.3%). Both cases of RCC died from their disease.

Among the eight families, five different *BAP1* PVs were identified (Figure 1), where none has been reported in the general population. Interestingly, all the PVs identified in the Swedish families are located in the first part of the gene, four of them are null variants, predicted to lead to a truncated protein lacking several important binding domains downstream or to activate nonsense-mediated RNA decay (NMD) of the aberrant transcripts (Figure 1). The fifth variant (His94Arg) is a missense variant located in the ubiquitin carboxy-terminal hydrolase (UCH)-domain. In a comprehensive study including known PVs (Walpole et al.2018), all of the *BAP1* missense variants classified as likely pathogenic were actually located in the UCH-domain [17]. All but one PV, c.669C > A (p.(Tyr223*), have been previously reported [17,21]. The Tyr223* variant is considered pathogenic and was identified in a proband that at an age of 46 had been diagnosed with several tumors, including CM, BIMT, and bilateral breast cancer. In the relatives, several other tumors had also been diagnosed (Table 2). This PV is a nonsense variant introducing a premature termination codon in exon 9 of the *BAP1* gene.

Three families (of which one has been previously reported [17]) have been identified with the same PV, c.58_59insTG (p(Glu20Valfs*53)), indicating a founder effect in Sweden for this variant that has, to our knowledge, not been identified in other countries. In the families with this PV, all the *BAP1* core tumors, beside RCC have been diagnosed (Table 2). This PV is located in exon 2 and is a 2-base-pair insertion causing a shift in the reading frame and subsequent introduction of a premature termination codon 53 amino acid downstream of the insertion.

Two families (of which one has been previously reported [17]) have been identified with the same PV, c.680_687delins13 (p.(Arg227Profs*6)). Also, this variant has not been reported outside Sweden. In these two families, all the *BAP1* core tumors, beside meningioma, have been diagnosed (Table 2). This pathogenic frame-shift variant is also located in exon 9 and leads to a truncated protein or to NMD.

Further, two families with different variants, c.79insG (p.(Val27fs)) and c.281A > G, (p.(His94Arg)), have been previously reported where the former has only been detected in Sweden and the latter is in a family with members living in both Sweden and Finland [17,21,22]. The first is a null variant, caused by a 1-base-pair insertion in exon 3, causing a frameshift and a premature stop codon. The latter is a missense variant in exon 5 that is considered as likely pathogenic. It is located in the middle of the UCH-domain and functional studies *in vitro* shows that the His94Arg variant almost entirely abolish the deubiquitinating activity [22]. In both families, several *BAP1* core tumors have been diagnosed (Table 2).

The segregation patterns in the *BAP1* families are presented in Supplementary Table S1. To summarize, for each of the PVs, several individuals with *BAP1* core tumors have been tested positive for *BAP1* PV (2–10 members for each of the PVs). In none of the *BAP1* PV families, there has been a 'phenocopy', e.g., a *BAP1* wt member with any of the *BAP1* core tumors (uveal melanoma, cutaneous melanoma, BIMT, mesothelioma, meningioma, or renal cell cancer). A lesser number of individuals without *BAP1* core tumors has been available for *BAP1* testing (1–6 members for each of the PVs).

Table 2. Tumors in *BAP1* pathogenic variant carrying families identified in Sweden.

Family nr: cDNA change (protein change)	Cutaneous melanoma	Uveal melanoma	BIMT	Meso-thelioma	Meningioma	Renal cell cancer	Basal cell carcinoma	Other tumors (age at diagnosis), tumor-related death†
S-138: c.58_59insTG, p(Glu20Valfs*53)								
Number of individuals with diagnosis in family, *n*	1	1	1	0	1	0	2	Thymus (56 y), Bladder (60 y), Lung† (70 y), Sarcomatous tumor† (66 y)
Youngest age at diagnoses, years	53y	38y	11y	–	40y	–	54y	
Tumor-associated deaths, *n*	0	0	0	–	0	–	0	
S-442: c.58_59insTG, p(Glu20Valfs*53)								
Number of individuals with diagnosis in family, *n*	0	1	2	1	0	0	0	Breast (56 y), Hypophysis (45 y), Pancreatic† (67 y)
Youngest age at diagnoses, years	–	40y	51y	52y	–	–	–	
Tumor-associated deaths, n	–	0	0	1	–	–	–	
S-446: c.58_59insTG, p(Glu20Valfs*53)								
Number of individuals with diagnosis in family, *n*	1	0	1	1	0	0	2	Pancreatic† (49 y)
Youngest age at diagnoses, years	35y	–	32y	50y	–	–	39y	
Tumor-associated deaths, *n*	0	–	0	1	–	–	0	
S-163: c.79insG, p.(Val27fs)								
Number of individuals with diagnosis in family, *n*	1	3	2	0	0	0	4	Prostate (67 y), Parotis (55 y), Lymphoma (62 y)
Youngest age at diagnoses, years	56y	16y	27y	–	–	–	50y	
Tumor-associated deaths, *n*	0	3	0	–	–	–	0	
S-164: c.281A > G, p.(His94Arg)								
Number of individuals with diagnosis in family, *n*	2	2	0	2	0	0	2	
Youngest age at diagnoses, years	Unknown	34y	–	60y	–	–	54y	
Tumor-associated deaths, *n*	1	1	0	2	–	–	0	
S-403: c.669C > A, p.(Tyr223*)								
Number of individuals with diagnosis in family, *n*	1	0	1	0	1	0	1	Breast (44 y), Bile duct adenoma (72 y), Prostate (74 y)
Youngest age at diagnoses, years	45y	–	10y	–	61y	–	76y	
Tumor-associated deaths, *n*	0	–	0	–	0	–	0	
S-162: c.680_687delins13, p.(Arg227Profs*6)								
Number of individuals with diagnosis in family, *n*	2	0	3	1 (*in situ*)	0	1	3	Lung cancer (77 y), Cutaneous squamous cell cancer (74 y)
Youngest age at diagnoses, years	44y	–	11y	39y	–	66y	49å	
Tumor-associated deaths, *n*	0	–	0	0	–	1	0	
S- 600: c.680_687delins13, p.(Arg227Profs*6)								
Number of individuals with diagnosis in family, *n*	4	1	2	2	0	2	0	Breast (56 y)
Youngest age at diagnoses, years	20y	75y	10y	54y	–	69y	–	
Tumor-associated deaths, *n*	0	0	0	2	–	1	–	

†Death from the tumor.

The members tested as carriers that have no diagnoses of any *BAP1* core tumor are all still at a rather young age (<55 years). Another aspect is that germline missense *BAP1* variants have recently been associated with a rare syndromic neurodevelopmental disorder (NDD) [23]. In the identified *BAP1* families in Sweden, there is no known case of NDD.

Discussion

To summarize, our study shows that in CM families lacking the other typical *BAP1* core tumors, *BAP1* PV variants are extremely uncommon (0% of the Swedish families). This is in line with findings from a Dutch study where *BAP1* PVs were found in 0.7% of CM families, however, two of the identified families also had BIMTs [24]. Further, in a large English cohort of CM families, deleterious *BAP1* variants were found in 0.2% of families, but also here, the pedigrees of carrier families revealed other *BAP1* core tumors [25]. Similar findings have been reported in samples of CM families from Denmark, Australia, and USA, with *BAP1* PVs present in well below 1% of CM families [15,16,26]. In a study from Finland, *BAP1* PVs were found in 25% of UM families. Further, in rare families with multiple cases of mesothelioma, *BAP1* PVs are prevalent [12,27,28]. In the Swedish families included, presenting with different *BAP1* core tumors, a significant portion (16%) was identified with *BAP1* PVs. In fact, in families having BIMT together with any other core tumor, *BAP1* germline mutations are so prevalent (>85% of the Swedish families), that in such families, *BAP1*-TPDS should always be suspected. Similarly, families presenting with both UM and mesothelioma that are both uncommon tumors in the normal population should always raise suspicion of *BAP1*-TPDS. Of note, neither the Sanger sequencing nor the IonAmpliSeq method used in our study has the potential to detect structural rearrangements or copy number changes (larger deletions or duplications). Hence, it is likely that if such a family exists in our cohort, it would have been missed. Still there have been very few families detected with such large germline *BAP1* aberrations, to our knowledge only one family with a large deletion [17,29].

The strength of the study is the population-based setting, with testing on a national level for the *BAP*1 mutation. A possible bias is that our clinical and research focus is on melanocytic tumors and skin tumors (CM, UM, BIMT, BCC), hence, potential families presenting with only the other *BAP1* core tumors (mesothelioma, RCC, or meningioma), could therefore have been missed. The tumors that are typical for the *BAP1*-TPDS are usually diagnosed and followed-up by different healthcare specialists (dermatologists, ophthalmologists, lung specialists, urologists, neurologists, oncologists

etc.). This study hopefully contributes to an increased awareness among medical professionals that encounter patients with personal and family history of these specific tumors that should be referred for genetic testing. Identification of families with a germline *BAP1* PV is essential for early detection and appropriate surveillance for individuals that are at high risk for a broad spectrum of tumors. Our study supports the initiation of dermatologic follow-up of *BAP1* carriers in early adolescence because skin tumors (CM, BIMT and BCC) are invariably seen in the families and can present at a young age. Similarly, to initiate ophthalmologic controls in early adulthood (or in adolescence in families with very young case(s)) appears rational, considering the early onset of UM that was seen in some of the carriers. In our study, RCC was only seen among two carriers of one of the specific PVs, Arg227Profs*6 both in their late sixties, but were advanced tumors since the patients died from their disease. In the comprehensive study from 2018, lower incidence of RCC was also seen, compared to CM, UM, and mesothelioma [17]. With the current knowledge we argue toward that RCC screening (ultrasound or MRI) should be directed toward those with a family history of RCC or PVs known to be associated with this tumor, starting at age 40, or 10 years earlier than the earliest case in the family. There are to date no screening modalities that have been established in the screening for mesothelioma [30]. However, due to the high incidence of different tumors (also other than the core tumors), there should be a low threshold to initiate directed investigations (radiology, endoscopy, pathology etc.) in carriers presenting with different symptoms. To conclude, in Sweden, *BAP1* mutations are found in families presenting with specific tumors where members require directed counseling and surveillance. This study has further contributed to the setting of the national recommendations for genetic testing and surveillance of *BAP1* families in Sweden [31].

Disclosure statement

No potential conflict of interest was reported by the authors

Funding

This work was supported by grants from the Swedish Cancer society [20 0156 F and 21 1486 Pj], ALF grant from Region Stockholm [grant number FoUI-954830 and FoUI-975235] and the Cancer Research Funds of Radiumhemmet [grants numbers 194092 and 2240233 (HH) and 174172 and 194103 (VH)].

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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